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09/601,490	09/21/2000	Desire Jose Collen	702-001463	5827

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/601,490	Applicant(s) COLLEN, DESIRE JOSE	
	Examin r Delia M. Ramirez	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-62* is/are pending in the application.

4a) Of the above claim(s) *31-38,42,44,48-50 and 52-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-41,43,45-47,61 and 62* is/are rejected.

7)☒ Claim(s) *51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Application

Claims 31-62 are pending.

Applicant's amendment of claims 39-41, 43, 45-47, 51, addition of claims 61-62 and submission of an amended Abstract in Paper No. 15, filed on 11/12/2002 is acknowledged.

This application contains claims 31-38, 42, 44, 48-50, 52-60 drawn to an invention non-elected with traverse in Paper No. 12, filed on 2/15/2002. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

1. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to EPO application No. 98200323.8 filed on 2/4/1998 and EPO application No. 98200365.9 filed on 2/6/1998.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on 11/12/2002 was filed after the mailing date of the first Office Action on the merits on 5/7/2002. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

3. The drawings have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

4. Claim 43 is objected to because it is directed to non-elected inventions. Specifically, claim 43 is directed to all the staphylokinase derivatives listed in Tables 1, 3-8, 13, 19 and 20. Applicants were advised in Paper No. 13, page 3, first paragraph of the Action, that claim 43 should be amended since it encompasses other staphylokinase derivatives not elected. For examination purposes, the term "listed in Tables 1, 3-8, 13, 19 and 20" will not be given patentable weight. Appropriate correction is required.

5. Claims 61-62 are objected to because of the recitation of "wherein the at least one amino acid substituted with Cys". For clarity, it is suggested that the term "at least one" be deleted" . Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 39-41, 43, 45-47, 51, 61-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 39-41 (claims 43-47, 51, 61-62 dependent thereon) are indefinite in the recitation of "derivative having essentially the amino acid sequence as depicted in Figure 1 (SEQ ID NO: 1)" since the term "having essentially the amino acid sequence.." is a relative term and neither the claim nor the specification provide a standard for ascertaining the requisite degree. As written, one cannot determine if the staphylokinase derivative of SEQ ID NO: 1 is one where amino acid residues can be added or deleted and how many, which amino acids can be substituted and how many can be substituted. Therefore one of skill in the art cannot reasonably apprised of the scope of the invention. For examination purposes, the term "derivative having essentially the amino acid sequence as depicted in Figure 1 (SEQ ID NO: 1)" will be interpreted as "any staphylokinase". Correction is required.

9. Claim 39 (claims 40-41, 43, 45-47, 51 and 61-62 dependent thereon) is indefinite in the recitation of "amino acid sequence as depicted in figure 1 (SEQ ID NO: 1) reactivity with panel of .." as it is unclear what the meaning of the phrase is. First, there is no connection between the term "amino acid sequence" and the term "reactivity". Second, as written, one cannot clearly establish which monoclonal antibodies are part of the panel recited. For examination purposes, it will be assumed that the claim is directed to any staphylokinase which can react with any murine monoclonal antibody which is specific towards any staphylokinase. Correction is required.

10. Claims 46-47 are indefinite in the recitation of "derivatives of claim 45 wherein (a) selected amino acids in the NH_2-terminal region of 10 amino acids (SEQ ID NO: 1 positions 1-

10)" and "derivative as claimed in claim 46, wherein the Ser in position 2 or 3 (SEQ ID NO:1)", respectively, for the following reasons. Claims 46 and 47 ultimately depend upon claim 39, which is drawn to any staphylokinase (see above for claim interpretation). As such, recitation of specific positions within SEQ ID NO: 1 is indefinite since the staphylokinase of claim 39 (claims 46 and 47 dependent thereon) does not have the sequence of SEQ ID NO: 1 and its sequence may not even have the same amino acid residue length.. For examination purposes, the term "derivatives of claim 45 wherein (a) selected amino acids in the NH2-terminal region of 10 amino acids (SEQ ID NO: 1 positions 1-10)" will be interpreted as "the staphylokinase of SEQ ID NO: 1 wherein selected amino acid residues at positions 1-10 are substituted with Cys". Similarly, the term "derivative as claimed in claim 46, wherein the Ser in position 2 or 3 (SEQ ID NO: 1)" will be interpreted as "staphylokinase of SEQ ID NO: 1 wherein the Ser in position 2 or 3 is substituted with a Cys". Correction is required.

11. Claim 61 is indefinite in the recitation of "amino acid substituted with Cys is at least one of a surface exposed residue" as it is unclear what the meaning of the term "at least one of a surface exposed residue" is within the context of the claim. For examination purposes, the term "at least one of a surface exposed residue" will be interpreted as "a surface exposed residue". Correction is required.

12. Claim 62 is indefinite in the recitation of "amino acid substituted with Cys is the position of the polyethylene glycol coupling" since it is unclear how an amino acid can be a position. It is suggested that if the intended meaning of the phrase is "polyethylene glycol coupling is introduced at the same position wherein the amino acid substitution takes place", the claim be

amended accordingly. For examination purposes, the interpretation above will be used.

Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 39-41, 43, 45-47, rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

15. Claims 39-41, 43, 45-47, 61-62 are drawn to a genus of staphylokinase derivatives wherein (1) at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys and/or (2) polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope. Claim 61 adds the limitation that the amino acid substituted is a surface-exposed residue (i.e. a residue which is exposed to the medium surrounding the protein). While the claims as originally filed were drawn to a genus of staphylokinase derivatives wherein (1) at least one amino acid is substituted with Cys and/or (2) polyethylene glycol is linked to the staphylokinase derivatives, there is no disclosure in the specification of staphylokinases derivatives which have been explicitly defined as staphylokinases wherein (1) at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys and/or (2) polyethylene glycol is coupled to an

amino acid residue which is outside both the binding epitope and the activation epitope. Similarly, there is no disclosure of staphylokinase derivatives which have been explicitly defined as staphylokinases wherein one of the amino acid residues substituted with Cys is a surface exposed residue. There is no disclosure in the specification of where the binding epitope and the activation epitope are or which amino acids are surface-exposed amino acids either. In addition, there is no mention in the specification of the genus of staphylokinase derivatives in the amended claims as preferred embodiments of the instant invention. Applicant is required to cancel the new matter in the reply to this Office Action.

16. Claims 39-41, 43, 45-47, 61-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 39-41, 43, 45-47, 61-62 are drawn to a genus of staphylokinases wherein (1) at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys and/or (2) polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope. Claims 40 and 43 add the limitation that the staphylokinase would have one or more amino acids substituted so that there is a reduction in absorption by SakSTAR-specific antibodies. Claim 41 adds the limitation that one or more amino acids have been substituted so that the specific activity is at least 50% that of the corresponding wild-type staphylokinase. Claim 61 adds the limitation that at least one of the amino acid substituted is a surface exposed residue. While the specification discloses some

staphylokinases which are derivatives of the staphylokinase from S. aureus wherein some amino acid residues have been replaced with Cys and wherein polyethylene glycol has been linked to some residues of such derivatives, the specification fails to disclose (1) other staphylokinases as encompassed by the claims from other organisms, (2) the binding epitope or the activation epitope in any staphylokinase, (3) which amino acid residues can be substituted with Cys in any staphylokinase and still retain at least 50% of the specific activity of the corresponding wild-type staphylokinase, (4) which are the surface exposed residues in a staphylokinase and which of these surface exposed residues can be substituted without losing activity.

While one could argue that the staphylokinases of the instant claims are adequately described since one can isolate and/or make staphylokinase derivatives by sequence comparison using the polypeptide structures disclosed in the instant application or the prior art, the state of the art teaches that small amino acid changes can drastically change the function of a polypeptide. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The specification only discloses a few species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the genus. Thus, one skilled in the art cannot

reasonably conclude that Applicant had possession of the claimed invention at the time the instant application was filed.

17. This rejection was applied to claims 39-41, 45-46 in previous Office Action Paper No. 13, mailed on 5/7/2002 and is now also applied to amended claims 43, 47 and newly added claims 61-62.

18. Applicant argues that claim 39 as amended is now directed to staphylokinase derivatives wherein the amino acid substitution with Cys is restricted to positions outside both the binding epitope and the activation epitope and that such epitopes are known in the art. Furthermore, Applicant argues that the added limitations are a convenient way to refer to the individual substitutions enabled by the specification. Similarly, Applicant argues that claim 39 as amended further limits the claims in regard to where polyethylene glycol can be coupled. It is Applicant's opinion that these limitations provide sufficient guidance so that undue experimentation would not be required to determine which staphylokinase derivatives would have at least 50% of the specific activity of the corresponding wild-type staphylokinase.

19. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. The genus of staphylokinases claimed is not adequately described for the reasons discussed above. In regard to Applicant's assertion that the binding epitopes and activation epitopes are known in the art, it is noted that while Jespers et al. (Thromb. Haemost. 81:479-485, April 1999; cited in the IDS) discloses "binding and activation epitopes" for SakSTAR, there is no disclosure of such epitopes for other members of the genus of staphylokinases encompassed by the claims. Also, it is noted that the teachings of Jespers et al. were disclosed after the priority date claimed in the instant application. There is no disclosure

of which amino acids can be replaced with Cys in other staphylokinases and retain at least 50% of the specific activity found in the corresponding wild-type staphylokinase. Therefore, in view of the information provided, one cannot reasonably conclude that the claimed invention is adequately described.

20. Claims 39-41, 43, 45-47, 61-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the staphylokinase variant labeled SY19 (S3C-MP5), does not reasonably provide enablement for (1) any staphylokinase wherein at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys and/or polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope, (2) any staphylokinase wherein at least one surface exposed residue outside both the binding epitope and the activation epitope is substituted with Cys and/or polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope or (3) any staphylokinase wherein at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys so that its activity is at least 50% that of the corresponding wild-type staphylokinase, and/or polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or

guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims is not commensurate with the enablement provided in regard to the extremely large number of unknown staphylokinases encompassed by the claims. As indicated above (see claim interpretation in claim rejections under 35 USC 112, second paragraph), claim 39 is drawn to any staphylokinase which has at least one amino acid substituted with Cys at a position outside both the binding epitope and the activation epitope and/or polyethylene glycol coupled to an amino acid residue outside both the binding epitope and the activation epitope. The specification discloses some S. aureus staphylokinase (SakSTAR) derivatives wherein some amino acid residues have been replaced with Cys and wherein polyethylene glycol has been linked to some residues of such derivatives. However, the specification fails to disclose other staphylokinases as encompassed by the claims from other organisms, the binding or activating epitopes in such staphylokinases, the amino acid residues which can be substituted with Cys and still retain at least 50% of the specific activity found in the corresponding wild-type staphylokinase, which are the surface exposed residues in a staphylokinase and which of these surface exposed residues can be substituted without inactivation of the staphylokinase.

As indicated above, the state of the art teaches that small changes can severily affect the function of a polypeptide as evidence by the teachings of Broun et al. (Science 282:1315-1317, 1998), Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed. Therefore, some knowledge or guidance

as to how structure is related to function is required to obtain staphylokinases which are functional and have the desired functional characteristics. A skilled artisan would have to know which are the binding and activating epitopes as well as the surface exposed residues in any staphylokinase to make the claimed derivatives.. It is important to note that there is no information in the specification as to whether any amino acid outside the binding epitope and the activation epitope can be substituted with Cys without inactivation of the staphylokinase or without losing more than 50% of the specific activity of the corresponding wild-type staphylokinase. Similarly, there is no disclosure in the specification as to whether any surface-exposed amino acid can be substituted with Cys without inactivation of the staphylokinase or without losing more than 50% of the specific activity of the corresponding wild-type staphylokinase. Therefore, due to the amount of information provided, the lack of knowledge about the binding and activating epitopes in any staphylokinase, the lack of knowledge in regard to surface exposed residues in any staphylokinase, and the unpredictability of the prior art in regard to small changes and how they affect function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to make and use the claimed staphylokinases, as encompassed by the claim. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

21. This rejection was applied to claims 39-41, 45-46 in previous Office Action Paper No. 13, mailed on 5/7/2002 and is now also applied to amended claims 43, 47 and newly added claims 61-62.

22. Applicant argues that claim 39 as amended is now directed to staphylokinase derivatives wherein the amino acid substitution with Cys is restricted to positions 1-10, and polyethyleine glycol substitution is also limited to the Cys components of the claimed derivatives. As such, these limitations provide sufficient guidance so that undue experimentation would not be required to determine which staphylokinase derivatives would have at least 50% of the specific activity of the corresponding wild-type staphylokinase.

23. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. It is noted that the scope of claim 39 as amended is not limited to derivatives which result from amino acid substitutions at positions 1-10 of SEQ ID NO: 1, as asserted. Instead, the scope of claim 39 encompasses any staphylokinase wherein (1) at least one amino acid residue outside both the binding epitope and the activation epitope is substituted with Cys and/or (2) polyethylene glycol is coupled to an amino acid residue which is outside both the binding epitope and the activation epitope. See claim interpretation in claim rejections under 35 USC 112, second paragraph. Therefore, since the scope of the instant claims is not commensurate with the enablement provided for the reasons discussed above, one cannot reasonably conclude that the specification provides sufficient information to enable of skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 39-41 were rejected under 35 U.S.C. 102(e) as being anticipated by Behnke et al. (US Patent No. 5801037).

25. This rejection has been discussed at length in Paper No. 13, mailed on 5/7/2002.

26. Applicant argues that claims 39-41 as amended are not anticipated by Behnke et al. since there is no indication that the compound of Behnke et al. allows for dimerization and/or increased specific activity and/or reduced clearance and/or increased thrombolytic potency. Furthermore, Applicants assert that the amino acid substituted in the polypeptide of Behnke et al. is Met at position 26, which according to Applicant is within the binding domain of the staphylokinase.

27. While it is agreed that Behnke et al. does not disclose their compound as having the ability to dimerize, increased specific activity, reduced clearance, and/or increased thrombolytic potency, these are characteristics which would be inherent to the product. Also, it appears that Applicant refers to "binding domain of the staphylokinase" as being equivalent to "binding epitope", therefore it will be assumed that Applicant asserts that position 26 is within the "binding epitope". In view of the fact that the claims are now further limited in regard to the location of the amino acid substitution with Cys and taking into consideration Applicant's assertion in regard to position 26 of the staphylokinase of Behnke et al., this rejection is hereby withdrawn.

Double Patenting

28. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

29. Claims 39-41, 43, 45, 61-62 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5 of U.S. Patent No. 6383483. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claim 39 of the instant application is drawn to any staphylokinase which has at least one amino acid substituted with Cys at a position outside both the binding epitope and the activation epitope and/or polyethylene glycol coupled to an amino acid residue outside both the binding epitope and the activation epitope. Claims 40, 41 and 43 add the limitation that the staphylokinase has reduced absorption of SakSTAR-specific antibodies or that the staphylokinase has a specific activity which is at least 50% that of the corresponding wild-type staphylokinase. Claim 61 adds the limitation that the residue to be substituted should be a surface exposed residue, a charged residue, a Thr residue, or a Ser residue. Claims 3-5 of U.S.

Patent No. 6383483 are directed to a staphylokinase derivative which comprises an amino acid sequence which differs from that of wild-type SakSTAR by one amino acid substitution at position 109 with Cys. The specification of U.S. Patent No. 6383483 teaches that this SakSTAR derivative (K109C) has an specific activity which is comparable to that of the wild-type staphylokinase and also teaches that this derivative has reduced absorption of SakSTAR specific antibodies. Also, the amino acid at position 109 is a Lys residue (prior to substitution with Cys), which is a charged residue. Furthermore, according to the teachings of Jespers et al. (Thromb. Haemost. 81:479-485, April 1999; cited in the IDS), position 109 of SakSTAR is not part of the binding or activation epitopes of SakSTAR. Therefore, the staphylokinase of U.S. Patent No. 6383483 anticipates claims 39-41, 43, 61 as written.

Claims 45 and 62 of the instant application are drawn to the staphylokinase of claim 39 as described above wherein the Cys is chemically modified with polyethylene glycol which can have a molecular weight of up to 20 KDa or to the staphylokinase of claim 39 wherein coupling of polyethylene glycol takes place at the same position as that where the amino acid substitution takes place. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Cys at position 109 of the staphylokinase K109C by coupling polyethylene glycol to that Cys for the benefit of reducing the immunogenicity of such staphylokinase as well as its plasma half life, since it is known in the art that pegylation (i.e. coupling of polyethylene glycol to amino acid residues) may interfere with antigen processing and may also delay antibodies and proteolytic enzymes from further degradation of a protein. One of skill in the art has a reasonable expectation of success at coupling polyethylene glycol to an amino acid residue since this chemical modification is well known and widely used in the art.

Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

30. Claims 39-41, 43, 45, 61-62 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7-8 of copending Application No. 09/728670. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim not is patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each for the following reasons.

Claim 39 of the instant application is drawn to any staphylokinase which has at least one amino acid substituted with Cys at a position outside both the binding epitope and the activation epitope and/or polyethylene glycol coupled to an amino acid residue outside both the binding epitope and the activation epitope. Claims 40, 41 and 43 add the limitation that the staphylokinase has reduced absorption of SakSTAR-specific antibodies or that the staphylokinase has a specific activity which is at least 50% that of the corresponding wild-type staphylokinase. Claim 61 adds the limitation that the residue to be substituted should be a surface exposed residue, a charged residue, a Thr residue, or a Ser residue. Claims 45 and 62 of the instant application are drawn to the staphylokinase of claim 39 as described above wherein

the Cys is chemically modified with polyethylene glycol which can have a molecular weight of up to 20 KDa or to the staphylokinase of claim 39 wherein coupling of polyethylene glycol takes place at the same position as that where the amino acid substitution takes place.

Claims 7 and 8 of copending Application No. 09/728670 are directed to staphylokinase derivatives having an amino acid substituted with Cys and to staphylokinases having polyethylene glycol coupled to amino acid residues of such staphylokinases, respectively. The specification of copending Application No. 09/728670 discloses SakSTAR derivatives K109C and K102C as embodiments which provide support for claim 7 and it also discloses the pegylation of K102C as an embodiment which provides support for claim 8. Furthermore, the specification of copending Application No. 09/728670 also discloses that derivatives K109C, K102C, and K102-PEG (derivative K102C pegylated with a 5 KDa polyethylene glycol) have specific activities which are comparable to that of the corresponding wild-type staphylokinase (SakSTAR) and also teaches that these derivatives have reduced absorption of SakSTAR specific antibodies. Also, the amino acid at position 109 is a Lys residue (prior to substitution with Cys), which is a charged residue. Furthermore, according to the teachings of Jespers et al. (Thromb. Haemost. 81:479-485, April 1999; cited in the IDS), positions 102 or 109 of SakSTAR are not part of the binding or activation epitopes of SakSTAR. Therefore, one of skill in the art would conclude that the invention of claims 39-41, 43, 45, 61-62 of the instant application is an obvious variation of the invention in claims 7-8 of copending Application No. 09/728670 since the embodiments disclosed to provide support for claims 7-8 of copending Application No. 09/728670 are the subject matter being claimed in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Allowable Subject Matter

31. Claim 51 is allowable over the prior art of record but it is objected to since it is dependent upon rejected claim 47.

Conclusion

32. No claim is in condition for allowance.

33. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

34. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
January 30, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
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